Article 34

Claims

1. A binding molecule which is a recombinant polypeptide comprising:
(i) a binding domain capable of binding a target molecule, and
(ii) an effector domain having an amino acid sequence substantially homologous to all or part of a constant domain of a human immunoglobulin heavy chain;
wherein the binding molecule is capable of binding the target molecule without triggering significant complement dependent lysis, or cell mediated destruction of the target,
characterised in that the effector domain is
- capable of specifically binding FcRn and/or FcγRIIb, and
- a chimeric effector domain which is derived from two or more human immunoglobulin heavy chain C_H2 domains including a first human immunoglobulin heavy chain C_H2 domain wherein 2, 3 or 4 amino acids in at least 1 region of the C_H2 domain have been modified to the corresponding amino acids from a second, different, human immunoglobulin heavy chain C_H2 domain,

wherein the region is selected from the 2 discrete regions numbered residues 233-236, and 327-331 in accordance with the EU numbering system,

and wherein in each case the human immunoglobulin is selected from IgG1, IgG2 and IgG4.

2. A binding molecule as claimed in claim 1 wherein the first human immunoglobulin is selected IgG1, IgG2, and IgG4, and the second human immunoglobulin is selected from IgG2 and IgG4.

3. A binding molecule as claimed in claim 1 or claim 2 wherein 2 amino acids in 1 region of the C_H2 domain are modified to the corresponding amino acids from a second human immunoglobulin heavy chain C_H2 domain.

4. A binding molecule as claimed in any one of the preceding claims wherein at least 2 amino acids in each of the 2 discrete regions of the C_H2 domain are modified to the corresponding amino acids in the corresponding region in a second and third human immunoglobulin heavy chain C_H2 domain respectively.

5. A binding molecule as claimed in any one of the preceding claims wherein the effector domain shares at least

about 90% sequence identity with the first human immunoglobulin heavy chain C_H2 domain.

6. A binding molecule as claimed in any one of the preceding claims comprising a human immunoglobulin heavy chain C_H2 domain having one or more of the following amino acids or deletions at the stated positions in accordance with the EU numbering system:

Posn	Amino acid
233	P
234	V
235	A
236	(No residue) or G
327	G
330	S
331	S

7. A binding molecule as claimed in any one of the preceding claims comprising a human immunoglobulin heavy chain C_H2 domain having one or more of the following blocks of amino acids or deletions at the stated positions in accordance with the EU numbering system: 233P, 234V, 235A and no residue at 236; or 233P, 234V, 235A and 236G; and/or 327G, 330S and 331S.

8. A binding molecule as claimed in any one of claims 5 to 7 wherein the effector domain is selected from G1Δab, G2Δa or G1Δac.

9. A binding molecule as claimed in any one of the preceding claims further comprising modifications to render the molecule substantially null allotypic.

10. A binding molecule as claimed in any one of the preceding claims wherein the effector domain has a reduced affinity for FcγRI, FcγRIIa or FcγRIII and a reduced ability to mediate complement lysis by comparison with the first or second human immunoglobulin heavy chain C_H2 domain.

11. A binding molecule as claimed in claim 10 wherein the effector domain has retained an affinity for FcγRIIb.

12. A binding molecule as claimed in any one of the preceding claims wherein the binding domain derives from a different source to the effector domain.

13. A binding molecule as claimed in any one of the preceding claims wherein the binding domain is selected from the binding site of an antibody; an enzyme; a hormone; a receptor; a cytokine or an antigen; a ligand or an adhesion molecule.

14. A binding molecule as claimed in any one of the preceding claims wherein the binding domain is capable of binding any of: the RhD antigen of red blood cells; an HPA alloantigen of platelets; a neutrophil antigen; a T-cell receptor; integrin; GBM collagen; Der P1; HPA-1a; VAP-1; laminin; lutheran; platelet glycoprotein VI; platelet glycoprotein Ia/IIa.

15. A binding molecule as claimed in claim 14 wherein the binding domain is selected from that of CAMPATH-1 and FOG1; OKT3; B2 (anti-HPA-1a); VAP-1; murine anti-α3 (IV) NC1; YTH12.5 (CD3); 2C7 (anti-Der p I); anti-laminin; anti-lutheran.

16. An isolated nucleic acid comprising a nucleotide sequence encoding the effector domain of the binding molecule as claimed in any one of the preceding claims.

17. A nucleic acid as claimed in claim 16 wherein the nucleotide sequence encodes a binding molecule as claimed in any one of the preceding claims.

18. A nucleic acid as claimed in claim 16 or claim 17 which is a replicable vector.

19. A nucleic acid as claimed in claim 18 wherein the nucleotide sequence is operably linked to a promoter.

20. A host cell comprising or transformed with the vector of claim 19 or claim 20.

21. A process for producing a binding molecule as claimed in any one of claim 1 to 15, the process comprising the step of modifying a nucleotide sequence encoding a first human immunoglobulin heavy chain C_H2 such that 2, 3 or 4 amino acids in at least 1 region of the C_H2 domain corresponds to an amino acid from a second human immunoglobulin heavy chain C_H2 domain,

wherein the region is selected from the 2 discrete regions

numbered residues 233-236, and 327-331 in accordance with the EU numbering system,

and wherein in each case the human immunoglobulin is selected from IgG1, IgG2 and IgG4.

22. A process as claimed in claim 21 wherein 2 amino acids in 1 region of the C_H2 domain are modified to the corresponding amino acids from a second human immunoglobulin heavy chain C_H2 domain.

23. Use of a binding molecule or nucleic acid as claimed in any one of claims 1 to 19 to bind a target molecule with said binding molecule.

24. Use as claimed in claim 23 wherein the target molecule is FcγRIIb, which binding causes inhibition of one or more of: B cell activation; mast cell degranulation; phagocytosis.

25. Use as claimed in claim 24 to prevent, inhibit, or otherwise interfere with the binding of a second binding molecule to the target molecule.

26. Use as claimed in claim 25 wherein the second binding molecule is an antibody.

27. Use as claimed in claim 25 or claim 26 wherein the target molecule is selected from: the RhD antigen of red blood cells; an HPA alloantigen of platelets; a neutrophil antigen; a T-cell receptor; integrin; GBM collagen; Der P1; HPA-1a; VAP-1; laminin; lutheran; platelet glycoprotein VI; platelet glycoprotein Ia/IIa.

28. Use as claimed in any one of claims 24 to 27 for the treatment of a patient for a disorder selected from: Graft-vs-host disease; host-vs-graft disease; organ transplant rejection; bone-marrow transplant rejection; autoimmunity such as vasculitis, autoimmune haemolytic anaemia, autoimmune thrombocytopenia and arthritis; alloimmunity such as foetal/neonatal alloimmune thrombocytopenia; asthma and allergy; chronic or acute inflammatory diseases such as Chrohn's; HDN; Goodpastures, sickle cell anaemia, coronary artery occlusion.

29. Use as claimed any one of claims 23 to 28 wherein the binding molecule is administered to a patient, or optionally

in cases where the patient is an unborn infant, to the mother of the patient.

30. A pharmaceutical preparation comprising a binding molecule as claimed in one of claims 1 to 15, or a nucleic acid as claimed in any one of claims 17 to 19, plus a pharmaceutically acceptable carrier.

31. An oligonucleotide selected from:
MO22BACK: 5' TCT CCA ACA AAG GCC TCC CGT CCT CCA TCG AGA AAA 3'
MO22: 5' TTT TCT CGA TGG AGG ACG GGA GGC CTT TGT TGG AGA 3'
MO7BACK: 5' TCC TCA GCA CCT CCA GTC GCG GGG GGA CCG TCA GTC 3'
MO21: 5' GAC TGA CGG TCC CGC GAC TGG AGG TGC TGA GGA 3'